

which he touchingly referred to his contact with that survivor of Louis' pupils during his residence in Philadelphia. His presence in consultations was frequently sought by his former Philadelphia colleagues and pupils, and from Philadelphia he took his wife, the widow of Samuel W. Gross, in 1892.

I do not know how I can better close my consideration of Sir William Osler's five years' sojourn in Philadelphia than by a quotation from a poem which his friend, Dr. S. Weir Mitchell, addressed to him and read at a meeting of the

Charaka Club in New York in March, 1905* It was entitled "Books and the Man," and in it Mitchell refers with deep feeling to his first meeting with Osler and to the latter's years in Philadelphia. He wrote:

"Do you perchance recall when first we met—
And gaily winged with thought the flying night
And won with ease the friendship of the mind,—
I like to call it friendship at first sight.
"And then you found with us a second home,
And, in the practice of life's happiest art
You little guessed how readily you won
The added friendship of the open heart."

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THOROTRAST*

A NEW CONTRAST MEDIUM FOR RADIOLOGICAL DIAGNOSIS

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AS the method of examination by the roentgen ray has developed new weapons from time to time have been added to our armament, to aid us in obtaining greater knowledge of the various pathological lesions recorded on our fluoroscopic screen and photographic films. Barium sulphate was a far reaching advance over the older bismuth with its soluble salts; solutions of iodine used in retrograde pyelography were followed by Skiodan and Uroselectan, adding greatly to our knowledge of and ability to demonstrate lesions of the genito-urinary tract. The Graham-Cole method, devised to demonstrate function of the gall-bladder, opened up a new field, until to-day by use of the various preparations on the market gall-bladder disease is easily recorded and diagnosed. There still remained a large part of the human anatomy which was a closed book to us, or if we did by chance obtain any evidence of disease it was by the indirect method rather than by direct demonstration of the lesion in the viscus or viscera involved. We believe the time is fast approaching when we shall demonstrate lesions involving the liver, spleen, lymph glands, brain, arterial system, genito-urinary system, and to some extent the suprarenals, ovaries, bone marrow, and malposition of the placenta, as

easily as we carry out a routine gastro-intestinal examination to-day.

In the latter part of 1930 Paul Radt¹ discussed his method of the administration of thorium in a colloid solution of high dispersion and low or no toxicity, for the study of disease of the liver and spleen by the radiological method. From the early part of 1931, and still continuing, considerable research has been undertaken abroad with the new medium. In September, 1931, the Heyden Chemical Company requested us to carry out experimental work here, and very kindly placed at our disposal an unlimited supply of the solutions known as "Thorotrast" and "Umbrathor," at the same time forwarding us translations of the articles appearing in the continental journals shortly after their publication. We were immediately attracted by the possibility of solving problems by this method of examination, and enthusiastically accepted the offer.

In order that the investigations should be carried on from all angles we asked the co-operation of other departments. Professors W. E. Gallie and F. G. Banting assigned Drs. Ian Macdonald and D. A. Irwin^{2,3} to the clinical and medical research of this subject. These two workers have, during the winter, carried on a vast amount of research on the method of absorption, deposit, elimination, toxic reaction, radio-activity, and pathological changes

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in the viscus showing the greatest retention of the thorium, and any change in the blood picture which might point to an untoward result. We are very thankful to them for their work, and any quotations we may make from the clinical or animal research findings are given with full and grateful acknowledgment to them. Their articles appear in this issue of our *Journal*, and will give much added information from the histological, clinical, and pathological aspects.

Radt prepared a colloidal solution of 25 per cent thorium dioxide of high dispersion and low toxicity. This was injected intravenously, the solution having been previously heated to body temperature. The dosage will vary with the particular viscus to be studied, whether it be desired to obtain simply an outline of the liver or spleen, or whether a complete impregnation of these organs is desired. Doses of 10 to 20 c.c. will give simply structural outline, while doses of 75 to 80 c.c. will produce an appearance in the normal spleen and liver as if they were carved from limestone. It is possible to give 5 c.c. per kilo of body weight in rabbits without any ill effects, and, as we have obtained a solid white shadow of the liver and spleen in the human being with 0.8 per kilo of body weight, it will be understood that we are well below any danger line.

Thorotrast, or rather the thorium dioxide content, possesses the property of depositing itself throughout the cells of the reticulo-endothelial system. The liver, spleen, bone marrow and lymphatic glands, all receive relatively the same amount per gram of volume; smaller amounts are found in the adrenals and ovary; none has been demonstrated in the testicles. Occasionally, the kidney will show a slight deposit of the thorium dioxide in the intracellular spaces, but only if pre-existing disease is present, a normal kidney showing no retention. The lungs sectioned within a few days after administration of the thorium dioxide show a very sparse distribution of deposit, if no previously existing disease condition has obtained. This is simply an engulfing reaction. If a lesion is present the deposit is similar to that found in the diseased kidney. However, as time passes and elimination of the Kupffer cells through the central vein of the liver is established, these large cells are picked up in the blood stream, and carried through the right heart into the

lung. Irwin has demonstrated these cells in the upper part of the trachea lying on the surface, pointing to the elimination of the thorium dioxide by the respiratory system. This observation is, we believe, original on his part, none of the other investigators mentioning it in their work.

During the nine months that Drs. Macdonald and Irwin have been carrying out their observations no untoward reaction has occurred in any of the animals. Rabbits which were given their initial dose at the start of the investigation have been checked at frequent intervals for change in weight and any abnormality in hepatic or splenic function, and none whatever has been demonstrated. In fact, they appear as healthy and normal animals throughout the period. This finding corresponds with those of the continental workers, and we feel we may now state that no damage will result in the administration of thorium dioxide to the patient, particularly as the dosage used is so much smaller than the larger ones given to the control animals. In the animals sectioned from time to time, some within a few days after receiving their intravenous injection and others at intervals during the investigation, the last observations having been made only a few days ago, no microscopic evidence of structural change or damage can be demonstrated; all the sections of the various organs show perfectly normal structure, with the exception of the thorium deposit in the cells of the reticulo-endothelial system. Surely if any pathological change would occur, some microscopic evidence of it should be available now.

The question of the elimination of the thorium dioxide has undoubtedly been already asked by you. During the laboratory examinations no elimination of any appreciable amount was found during the first few weeks. In sections made of spleen, liver and bone marrow shortly after the administration of the thorium dioxide, minute deposits of the salt could be seen in the cells of the reticulo-endothelial system. As the weeks passed the Kupffer cells in the liver gradually increased in size, larger deposits of the thorium salt were present, and the cells appeared to migrate towards the central vein. In several sections these cells loaded with thorium dioxide were observed within the venous vessels of the liver, and as this phenomenon was noted the large cells became visible in the lung, definitely pointing toward

elimination from the liver by this route; at the same time the shadow of the liver became slightly less dense and in three months showed radiographically about 50 per cent of its original content. Sufficient time has as yet not elapsed to allow a statement as to the period required for complete elimination. The spleen, bone marrow, lymph glands, and ovary have as yet given no evidence of elimination. The thorium dioxide present in animals examined recently who have received their initial dosage at the commencement of this investigation, shows about the same amount present in these latter structures as the animals demonstrated within a few days of their initial reception of the salt.

Radioactivity has been proved to be absent. Films exposed for several days to heavily impregnated sections of liver and spleen show no reaction upon the films, the latter developing out as an absolutely unexposed film. Concentrated liver pulp of rabbits receiving large doses of thorium dioxide gave no reaction of any importance with the electroscope.

Thorium, as we know, possesses a very short wave length, and the wave length of its secondary radiation when bombarded by x-rays is also very short. With long-continued storage of the thorium dioxide in the liver and bone marrow, the question of exposure to radiation from the x-ray tube in cases suffering from metastases in these areas is an interesting one. At the present time Dr. Richards is carrying out research along these lines.

During the animal experiments and during the administration of the solution to patients, no reaction was observed in our work. Some investigators report slight rises in temperature accompanied by headache. This has always been stated to be so slight as to cause no alarm. If the solution be heated to body temperature and administered slowly these reactions will be eliminated. While these animal experiments were being carried out, and until we were satisfied that no harmful reaction could occur to the patient, we made a hard and fast rule that only patients past medical or surgical aid should receive thorotrast in our department. Only cases such as carcinoma with proved metastases in the liver were first used; then patients with extensive carcinoma of the stomach or bowel were given thorotrast, to

demonstrate the presence or absence of metastases; and later cases of typical cirrhosis of the liver received the drug and films were made.

TECHNIQUE

Our technique was as follows in these cases. A daily dose of 25 c.c. of thorotrast was administered intravenously for three days, a total of 75 c.c. in all being received by the patient. On the fourth day, films were made of the abdomen on the Potter-Bucky Diaphragm, and followed by films daily for several days, using the same time, distance, K.V. and M.A. factors until the greatest deposit of the dioxide was noted in the liver and spleen.

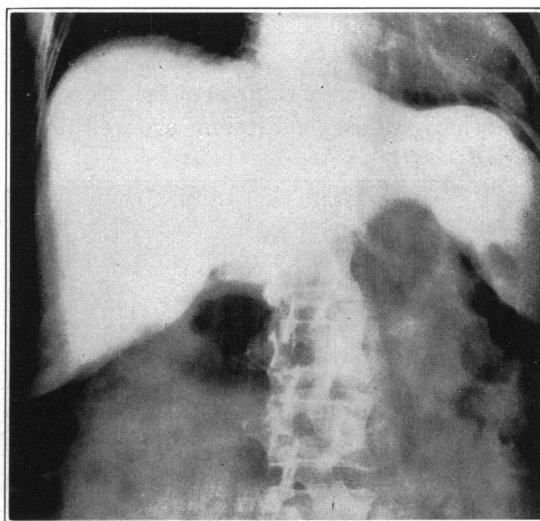


FIG. 1.—Normal liver and spleen impregnated with thorium dioxide.

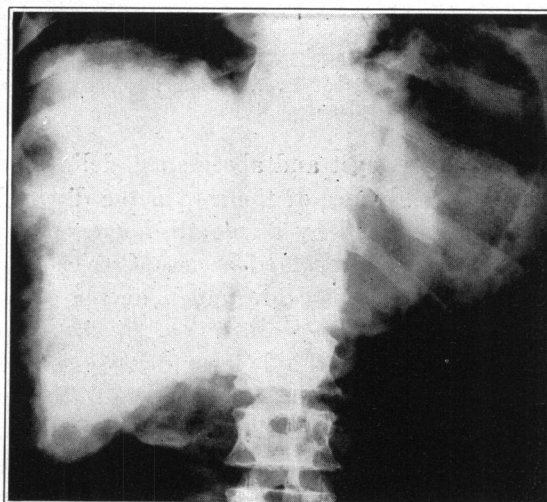


FIG. 2.—Marked metastases in liver. Note the honeycomb effect where no thorium dioxide has been deposited, indicating metastases.

A well outlined liver, smooth and homogeneous in density, we believe definitely rules out the presence of any carcinomatous change. Metastases are seen as areas lacking in thorium deposit and having a punched-out appearance. The spleen usually is shown as a smooth shadow of equal density throughout; complete absence of the spleen shadow may be due to thrombosis of the splenic artery, or to leukæmia. Enlargement of the spleen is very easily demonstrated. Several of our cases of cirrhosis accompanied by splenic enlargement were well demonstrated. Cysts and tumours of the spleen will show as negative shadows in the surrounding healthy spleen tissue; in other words, any damage to the reticulo-endothelial cells will cause an absence of thorium dioxide deposit.

Beside the metastases present so often in the liver, other pathological lesions are well demon-

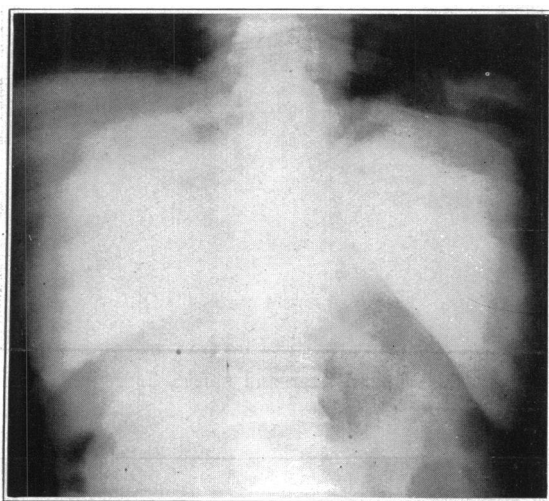


FIG. 3.—Cirrhosis of liver. Note decreased size of liver and enlarged spleen.

strated. Here, cyst and abscess are delineated by the utter absence of the salt in the diseased region, surrounded by a smooth, homogeneous shadow in the uninvolved areas. Cirrhosis of the liver shows a shadow much decreased in density, with the liver shrunk in size. At first we considered this lack of density due to the presence of ascites, but after the fluid had been removed our liver shadow was still below normal, and we concluded it was due to a general impairment of the absorptive action of the Kupffer cells. This method will also be found of great advantage in a differential diagnosis of abdominal tumour in the left and

right hypochondrium. How often have we laboured to differentiate spleen from kidney in tumour formation, or perhaps a tumour of the adrenal gland! A normal, well outlined spleen after the administration of the thorium dioxide, and the minute deposits in the adrenal gland, leave only the question of kidney or retro-peritoneal sarcoma. Pyelography will easily condemn or acquit the kidney, so by elimination a problem of this type should not present great difficulties. The study of the enlargement and shrinkage of the liver and spleen under different circulatory conditions has also been accomplished by this method. For a detailed account see the work of Paffenholz and Shuermever.⁴

If these were the only demonstrable uses for the new contrast medium we might well be satisfied, but the further application of this oxide to the diagnosis of disease in other systems and regions gives one the impression of having become the owner of Aladdin's lamp. Studies of the vessels of the brain have been carried out with brilliant results and no evidence of injury. Iodine and bromine, when used for this type of work, are not without disadvantages. Thorotrast is not toxic, produces no irritating effects, and possesses higher opacity than the bones of the skull. Patients suffering from arteriosclerosis tolerate its use extremely well, and as its administration is painless, no anæsthetic is needed. It also allows the films of the skull to be made in any direction; previously it could only be done with the head on either side. This allows an exact localization of any tumour or block in the arterial system.

To obtain stereoscopic films, 8 to 15 c.c. of thorotrast are introduced into the common carotid through a platinum needle, 1 mm. in diameter, bent or bayonet-pointed. The injection is given slowly and the exposures are made while the solution is flowing into the common carotid. The needle should lie well within the lumen of the artery and the injection preferably carried out from the right side. Several articles have been published by Moniz *et al.*⁵ where this method has been used in the study of brain tumours, atheromatous changes of the encephalic arteries, and in suspicious cases of meningitis, with absolutely no injury and brilliant results for the patient.

The same solution may be applied to the study of the arterial system of the limbs and the

abdominal aorta. After puncturing the artery with the platinum needle, the thorotrast is injected, the amount being 12 to 18 c.c., allowing about seven seconds for the injection, and films are made immediately. This period is needed to fill the arterial system. Localization of thrombosis, embolism, and development of collateral circulation may all be demonstrated.

The thorotrast solution may be used in retrograde pyelography. It is miscible with all body fluids without becoming flocculated. It is non-irritating and lacks the disadvantages of the iodine solution, as no cramps are produced, and the greater opacity of the salt produces a better radiogram than the iodide solution. In the examination of the urethra, on account of its thinner flowing, it will penetrate into the ducts of the urethral glands, fistulæ, and the opening of abscesses of the prostate. It is also of great advantage in the study of chronic prostatitis. Thorotrast also may be injected in various pathological lesions involving the lungs. Fistulous tracts in empyema are well outlined; bronchial fistula have been filled with the solution with no untoward effects. Bronchiectatic cavities of both the saccular and cylindrical types have been filled with the thorium dioxide, and as the solution has a not unpleasant taste it thus adds to its advantages. Kresmer,⁶ to test the harmlessness of the solution, filled the lung of an animal and left it for three months with no deleterious effects on the animal's health.

Obstetrics is also a debtor to this contrast medium. We are all aware of the difficulty in diagnosing placenta prævia and placenta

marginalis. Fortunately we have here a splendid aid. Ehrhardt⁷ in his experiments on white mice showed the placenta as round or oval discs, each placenta showed the same density, and he was able to foretell accurately the number of fetuses present. Liepmann,⁸ in the human being, by the use of thorotrast was able to demonstrate the size and position of the placenta. He administered various doses from 10 to 25 c.c. slowly, and obtained the outlines of the placenta.

In all of our patients, totalling now 18, who have received thorotrast during the last nine months, no unfavourable reaction has occurred, nor could any undesirable result be demonstrated. Some of the observers state that the solution is contraindicated in cirrhosis of the liver and marked damage to the spleen. Our experience with cirrhosis has been that no damage occurred to any patient whatsoever.

In conclusion, it is our firm belief that we have in this contrast medium one that is absolutely harmless to the patient and of invaluable aid in the diagnosis of lesions previously beyond us. With the advance it has made in the last eighteen months it is impossible to do more than speculate as to new uses for it in the future.

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MUCIN THERAPY FOR PEPTIC ULCER. — Brown, Cromer, Jenkinson and Gilbert, Chicago report that 36 out of 37 patients who had partial to complete disability on previous strict ulcer management were relieved objectively and subjectively by mucin. Roentgen deformities in topography were influenced more by administration of mucin than by former management. Emptying time or retention was diminished on mucin treatment. Disappearance of gross and occult blood in stomach and stools was more rapid with mucin treatment than with conventional management. Mucin treatment was effective in controlling several massive hæmorrhages from the stomach. Other methods were also effective. There have been no recurrences in 36 patients who had frequent previous recurrences. Hyperacidity, as measured by weekly Ewald test meals, was not lowered on the treatment of hourly feedings and powders and was only somewhat lowered by mucin treatment. All

the patients were taken off powders or mucin and food twelve hours previous to the test meal. Mucin in ordinary doses did not lower gastric acidity appreciably when placed in the stomach after a two hour fractional meal followed by aspirations at frequent intervals for from four to seven hours. In the mucin used the authors did not observe any secretagogue action which interfered with the beneficial effect. From their objective observations, the therapeutic effect is due to some factor other than neutralization of acid. There has been a notable increase in the feeling of well being and an improvement in the appearance and behaviour of the mucin-treated patients. The authors have found in the past that a majority of peptic ulcers heal with no treatment or any treatment. The minority are sometimes very resistant to the best forms of management. Mucin has helped these intractable cases.—*J. Am. M. Ass.*, 1932 99: 98.